--dup 39. **(Amended)** An isolated nucleic acid encoding an antibody CDR amino acid sequence of claim 4.

A2 44. **(Amended)** A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of claim 4, and a pharmaceutically acceptable carrier.

A3 54. **(Amended)** A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the antibody, or antigen-binding portion thereof, of claim 4 such that human IL-18 activity is inhibited.

A4 56. **(Amended)** A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the antibody, or antigen-binding portion thereof, of claim 4 such that human IL-18 activity in the human subject is inhibited.

A5 58. **(Amended)** A method for treating a human subject suffering from a disorder in which IL-18 activity is detrimental by administering an antibody according to claim 4 such that treatment is achieved.

REMARKS

Claims 39, 44, 54, 56, and 58 have been amended solely to reduce the number of multiple dependent claims. Accordingly, support for the amendments can be found in the specification and claims as originally filed. No new subject matter has been added.

Attached hereto is APPENDIX A, captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE". The attached Appendix includes a marked-up version of the changes made to the claims by current amendment. Upon entry of this amendment, claims 1-60, attached hereto in APPENDIX B, captioned "CLAIMS PENDING AFTER ENTRY OF PRELIMINARY AMENDMENT", will be pending.

SUMMARY

It is respectfully requested that the above amendment be entered. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-

identified application, the Examiner is urged to call Applicants' Attorney at the number listed below.

Respectfully submitted,

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Dated: July 25, 2001

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES

Claims 39, 44, 54, 56, and 58 have been amended as follows:

39. **(Amended)** An isolated nucleic acid encoding an antibody CDR amino acid sequence ~~of any one~~ of claim 4 ~~4-38~~.

44. **(Amended)** A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, ~~of any~~ of claim~~s~~ 4 ~~4-38~~, and a pharmaceutically acceptable carrier.

54. **(Amended)** A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the antibody, or antigen-binding portion thereof, ~~of any~~ of claim~~s~~ 4 ~~4-38~~ such that human IL-18 activity is inhibited.

56. **(Amended)** A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the antibody, or antigen-binding portion thereof, ~~of any~~ of claim 4 ~~4-38~~ such that human IL-18 activity in the human subject is inhibited.

58. **(Amended)** A method for treating a human subject suffering from a disorder in which IL-18 activity is detrimental by administering an antibody according to ~~any one of~~ claim 4 ~~4-38~~ such that treatment is achieved.

APPENDIX B

CLAIMS PENDING AFTER ENTRY OF PRELIMINARY AMENDMENT

1. A compound capable of binding a human IL-18 amino acid sequence, or portion thereof, wherein said amino acid comprises a sequence selected from the group consisting of SEQ ID NO: 67 and SEQ ID NO: 68.

2. The compound of claim 1, wherein said compound is selected from the group consisting of a small molecule, peptide, polypeptide, antibody, and antibody fragment.

3. The compound of claim 2, wherein said antibody, or antibody fragment, is fully human.

4. A human monoclonal antibody, or antigen-binding portion thereof, capable of binding to human IL-18.

5. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $0.1s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-6}M$ or less.

6. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-2}s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-7}M$ or less.

7. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-3}s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-8}M$ or less.

8. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-4} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of 1×10^{-9}M or less.

9. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-5} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of 1×10^{-10}M or less.

10. The antibody of claim 4, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-6} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of 1×10^{-11}M or less.

11. An isolated antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, comprising an amino acid sequence selected from the group comprising SEQ ID NO: 3 and SEQ ID NO: 33.

12. The antibody, or antigen-binding portion thereof, of claim 11, wherein the antibody is a neutralizing antibody.

13. The antibody, or antigen-binding portion thereof, of claim 11, which is a human antibody.

14. The antibody, or antigen-binding portion thereof, of claim 11, which is a recombinant antibody.

15. The antibody, or antigen-binding portion thereof, of claim 11, which is a monoclonal antibody.

16. An isolated antibody, or antigen-binding portion thereof, that binds to an epitope of human IL-18, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a k_{off} rate constant of $0.1 s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of 1×10^{-6}M or less.

17. The isolated antibody of claim 16, or an antigen-binding portion thereof, which dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-2} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-7} M$ or less.

18. The isolated antibody of claim 16, or an antigen-binding portion thereof, which dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-3} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-8} M$ or less.

19. The isolated antibody of claim 16, or an antigen-binding portion thereof, which dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-4} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-9} M$ or less.

20. The isolated antibody of claim 16, or an antigen-binding portion thereof, which dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-5} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-10} M$ or less.

21. The isolated antibody of claim 16, or an antigen-binding portion thereof, which dissociates from human IL-18 with a k_{off} rate constant of $1 \times 10^{-6} s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC_{50} of $1 \times 10^{-11} M$ or less.

22. An isolated human antibody, or an antigen-binding portion thereof, comprising at least one variable region CDR domain capable of binding an epitope of human IL-18.

23. The isolated antibody, or an antigen-binding portion thereof, of claim 22, wherein said antibody, or an antigen-binding portion thereof, contains at least one amino acid substitution or insertion that improves IL-18 binding as compared to the unmodified antibody or antigen-binding portion thereof.

24. The isolated antibody, or an antigen-binding portion thereof, of claim 22, wherein said antibody, or an antigen-binding portion thereof, contains at least one amino acid substitution or insertion that improves neutralization of IL-18 as compared to the unmodified antibody or antigen-binding portion thereof.

25. The isolated antibody, or an antigen-binding portion thereof, of claim 22, wherein said variable region comprises a CDR domain selected from the group consisting of:

a heavy chain CDR1 domain having an amino acid sequence of SEQ ID NO: 9, or sequence modified from SEQ ID NO: 9 by at least one amino acid substitution;

a heavy chain CDR2 domain having an amino acid sequence of SEQ ID NO: 10 , or sequence modified from SEQ ID NO: 10 by at least one amino acid substitution; and

a heavy chain CDR3 domain having an amino acid sequence of SEQ ID NO: 11, or sequence modified from SEQ ID NO: 11 by at least one amino acid substitution.

26. The isolated antibody, or an antigen-binding portion thereof, of claim 25, wherein said variable region comprises a CDR domain selected from the group consisting of:

a heavy chain CDR1 domain modified from SEQ ID NO: 9 by at least one amino acid substitution at position H30, H31, H32, H33, or H35;

a heavy chain CDR2 domain modified from SEQ ID NO: 10 by at least one amino acid substitution at position H52, H52a, H53, H54, H56, or H58; and

a heavy chain CDR3 domain modified from SEQ ID NO: 11 by at least one amino acid substitution at position H95, H96, H97, or H98.

27. The isolated antibody, or an antigen-binding portion thereof, of claim 22, wherein said variable region comprises a CDR domain selected from the group consisting of:

a light chain CDR1 domain having an amino acid sequence of SEQ ID NO: 12 , or sequence modified from SEQ ID NO: 12 by at least one amino acid substitution;

a light chain CDR2 domain having an amino acid sequence of SEQ ID NO: 13 , or sequence modified from SEQ ID NO: 13 by at least one amino acid substitution; and

a light chain CDR3 domain having an amino acid sequence of SEQ ID NO: 14 , or sequence modified from SEQ ID NO: 14 by at least one amino acid substitution.

28. The isolated antibody, or an antigen-binding portion thereof, of claim 27, wherein said variable region comprises a CDR domain selected from the group consisting of:

a light chain CDR1 domain modified from SEQ ID NO: 12 by at least one amino acid substitution at position L30, L31, L32, or L34;

a light chain CDR2 domain modified from SEQ ID NO: 13 by at least one amino acid substitution at position L50, L52, L53, or L55; and

a light chain CDR3 domain modified from SEQ ID NO: 14 by at least one amino acid substitution at position L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, or L97.

29. An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 16, and 17.

30. An isolated antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 16.

31. An isolated antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 17.

32. The isolated antibody, or an antigen-binding portion thereof, of claim 22, wherein said variable region comprises a CDR domain selected from the group consisting of:

a heavy chain CDR1 domain having an amino acid sequence of SEQ ID NO: 20 , or sequence modified from SEQ ID NO: 20 by at least one amino acid substitution;

a heavy chain CDR2 domain having an amino acid sequence of SEQ ID NO: 21 , or sequence modified from SEQ ID NO: 21 by at least one amino acid substitution; and

a heavy chain CDR3 domain having an amino acid sequence of SEQ ID NO: 22 , or sequence modified from SEQ ID NO: 22 by at least one amino acid substitution.

33. The isolated antibody, or an antigen-binding portion thereof, of claim 32, wherein said variable region comprises a CDR domain selected from the group consisting of:

a heavy chain CDR1 domain modified from SEQ ID NO: 20 by at least one amino acid substitution at position H30, H31, H32, H33, or H35;

a heavy chain CDR2 domain modified from SEQ ID NO: 21 by at least one amino acid substitution at position H50, H51, H52, H52a, H53, H54, H56, or H58; and

a heavy chain CDR3 domain modified from SEQ ID NO: 22 by at least one amino acid substitution at position H96, H96, H97, H98, H99, H100, H100a, H101, or H102.

34. The isolated antibody, or an antigen-binding portion thereof, of claim 32, wherein said variable region comprises a CDR domain selected from the group consisting of:

a light chain CDR1 domain having an amino acid sequence of SEQ ID NO: 23 , or sequence modified from SEQ ID NO: 23 by at least one amino acid substitution at position ;

a light chain CDR2 domain having an amino acid sequence of SEQ ID NO: 24 , or sequence modified from SEQ ID NO: 24 by at least one amino acid substitution; and

a light chain CDR3 domain having an amino acid sequence of SEQ ID NO: 25, or sequence modified from SEQ ID NO: 25 by at least one amino acid substitution.

35. The isolated antibody, or an antigen-binding portion thereof, of claim 34, wherein said variable region comprises a CDR domain selected from the group consisting of:

a light chain CDR1 domain modified from SEQ ID NO: 23 by at least one amino acid substitution at position L30, L31, L32, or L34;

a light chain CDR2 domain modified from SEQ ID NO: 24 by at least one amino acid substitution at position L50, L52, L53, or L55; and

a light chain CDR3 domain modified from SEQ ID NO: 25 by at least one amino acid substitution at position L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, or L97.

36. An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid selected from the group consisting of SEQ ID NO: 26, 27, and 29.

37. An isolated antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 29 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 26.

38. An isolated antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 29 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 27.

39. An isolated nucleic acid encoding an antibody CDR amino acid sequence of claim 4.

40. The isolated nucleic acid of claim 39, which is in a recombinant expression vector.

41. A host cell into which the recombinant expression vector of claim 40 has been introduced.

42. A method of synthesizing an antibody that binds human IL-18, comprising culturing the host cell of claim 41 in a culture medium until an antibody that binds human IL-18 is synthesized by the cell.

43. The method of claim 42, wherein said antibody is human.

44. A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of claim 4, and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44 which further comprises at least one additional therapeutic agent for treating a disorder in which IL-18 activity is detrimental.

46. The pharmaceutical composition of claim 45, wherein said additional agent is selected from the group consisting of an antibody, or fragment thereof, capable of binding human IL-12, methotrexate anti-TNF, corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.an

47. A method of making an antibody that binds human interleukin-18 (IL-18), comprising:

exposing an antibody repertoire to an antigen comprising an epitope of human IL-18 or portion thereof; and

selecting from the antibody repertoire an antibody that binds the epitope of human IL-18, or portion thereof.

48. The method of claim 47, wherein the antibody repertoire is an *in vivo* repertoire in an animal and the method comprises immunizing the animal with the antigen comprising an epitope of human IL-18 or portion thereof.

49. The method of claim 46 or 47, wherein said epitope comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 3 and 33.

50. The method of claim 47, wherein said *in vivo* repertoire is a fully human immunoglobulin repertoire integrated into the genome of the animal.

51. The method of claim 47, wherein the antibody repertoire is a recombinant antibody library and the method comprises screening the library with an antigen comprising the epitope of human IL-18 or portion thereof.

52. The method of claim 47, wherein the library is a human antibody library.

53. A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the compound of claim 1 such that human IL-18 activity is inhibited.

54. A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the antibody, or antigen-binding portion thereof, of claim 4 such that human IL-18 activity is inhibited.

55. A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the compound of claim 1 such that human IL-18 activity in the human subject is inhibited.

56. A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the antibody, or antigen-binding portion thereof, of claim 4 such that human IL-18 activity in the human subject is inhibited.

57. A method for treating a human subject suffering from a disorder in which IL-18 activity is detrimental by administering a compound according to claim 1 such that treatment is achieved.

58. A method for treating a human subject suffering from a disorder in which IL-18 activity is detrimental by administering an antibody according to claim 4 such that treatment is achieved.

59. The method of claim 57 or 58, wherein said disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthopathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthopathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis,

primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis C, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism (Hashimoto's disease), atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis ,vitiligo, acute liver disease, chronic liver diseases, allergy and asthma, mental disorders (*e.g.*, depression and schizophrenia) and Th2 Type and Th1 Type mediated diseases.

60. A method of treating a patient suffering from a disorder in which IL-18 is detrimental comprising the step of administering an anti-IL-18 antibody, before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an anti-IL-12 antibody or antigen binding fragment thereof, methotrexate, anti-TNF antibody or antigen binding fragment thereof, corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.